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published in

Clinical Nutrition
2019

DOI (link to publisher)

[10.1016/j.clnu.2018.07.023](https://doi.org/10.1016/j.clnu.2018.07.023)

document version

Publisher's PDF, also known as Version of record

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citation for published version (APA)

Reinders, I., Volkert, D., de Groot, L. C. P. G. M., Beck, A. M., Feldblum, I., Jobse, I., Neelemaat, F., de van der Schueren, M. A. E., Shahar, D. R., Smeets, E. T. H. C., Tieland, M., Twisk, J. W. R., Wijnhoven, H. A. H., & Visser, M. (2019). Effectiveness of nutritional interventions in older adults at risk of malnutrition across different health care settings: Pooled analyses of individual participant data from nine randomized controlled trials. *Clinical Nutrition*, 38(4), 1797-1806. <https://doi.org/10.1016/j.clnu.2018.07.023>

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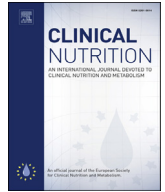
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Original article

Effectiveness of nutritional interventions in older adults at risk of malnutrition across different health care settings: Pooled analyses of individual participant data from nine randomized controlled trials

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ARTICLE INFO

Article history:

Received 15 January 2018

Accepted 15 July 2018

Keywords:

Dietary counseling
Oral nutritional supplements
Protein-energy malnutrition
Undernutrition
Weight gain

SUMMARY

Background & aims: Protein-energy malnutrition is a health concern among older adults. Improving nutritional status by increasing energy and protein intake likely benefits health. We therefore aimed to investigate effects of nutritional interventions in older adults (at risk of malnutrition) on change in energy intake and body weight, and explore if the intervention effect was modified by study or participants' characteristics, analysing pooled individual participant data.

Methods: We searched for RCTs investigating the effect of dietary counseling, oral nutritional supplements (ONS) or both on energy intake and weight. Principle investigators of eligible studies provided individual participant data. We investigated the effect of nutritional intervention on meaningful increase in energy intake (>250 kcal/day) and meaningful weight gain (>1.0 kg). Logistic generalized estimating equations were performed and ORs with 95% CIs presented.

Results: We included data of nine studies with a total of 990 participants, aged 79.2 ± 8.2 years, 64.5% women and mean baseline BMI 23.9 ± 4.7 kg/m². A non-significant intervention effect was observed for increase in energy intake (OR:1.59; 95% CI 0.95, 2.66) and a significant intervention effect for weight gain (OR:1.58; 95% CI 1.16, 2.17). Stratifying by type of intervention, an intervention effect on increase in energy intake was only observed for dietary counseling in combination with ONS (OR:2.28; 95% CI 1.90, 2.73). The intervention effect on increase in energy intake was greater for women, older participants, and those with lower BMI. Regarding weight gain, an intervention effect was observed for dietary counseling (OR:1.40; 95% CI 1.14, 1.73) and dietary counseling in combination with ONS (OR:2.48; 95% CI 1.92, 3.31). The intervention effect on weight gain was not influenced by participants' characteristics.

Conclusions: Based on pooled data of older adults (at risk of malnutrition), nutritional interventions have a positive effect on energy intake and body weight. Dietary counseling combined with ONS is the most effective intervention.

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Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio; ONS, oral nutritional supplements; RCTs, randomized controlled trials; SDs, standard deviations.

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<https://doi.org/10.1016/j.clnu.2018.07.023>

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1. Introduction

Protein-energy malnutrition is a significant health concern particularly affecting older adults. Its prevalence varies widely according to setting, i.e. less than 10% of independently living older adults are affected, whereas the prevalence increases up to 50% or more in nursing-home residents, geriatric patients in acute-care hospitals and patients in geriatric rehabilitation [1,2]. Malnutrition in older adults is associated with several adverse health and clinical outcomes, such as reduced strength, increased risk of morbidity (e.g. the development of pressure ulcers, impaired wound-healing, infectious complications, hospital readmissions and increased length of hospital stay), higher mortality risk [3–5], as well as higher health care costs [6].

Studies summarizing the overall effects of nutritional intervention strategies on health outcomes by increasing energy intake, i.e. through oral nutritional supplements (ONS), dietary counseling or both, showed limited effects [7–9]. Some studies showed that nutritional support in malnourished older patients may also lead to improved health outcomes, such as hand grip strength, physical activity levels, cognitive function or quality of life [10–16], while others have found no significant effects of nutritional interventions on health outcomes [10,17–19]. It may be possible that some nutritional intervention studies were not able to show improvements in health outcomes due to their low impact on energy intake or body weight, as this is a prerequisite for improving health outcomes. In addition, methodological shortcomings of some previous studies, such as small sample size, and differences between studies in setting, inclusion criteria and intervention strategies, may have contributed to the heterogeneity in study results [7]. Hence, it has been suggested to analyse individual participant data in order to take into account correlations of observations within studies and account for potential study bias [9]. A meta-analyses using aggregate data may overcome the shortcomings of individual studies [20] by allowing further investigation of treatment effects and interactions between treatment and factors such as study setting (hospital, community-dwelling, institutionalized), type of intervention (dietary counseling and/or ONS) or participants' characteristics.

In this study, we have pooled individual participant data from nine international nutritional intervention studies performed among older adults at risk of malnutrition. This study aims to examine 1) the effect of the intervention on meaningful increase in energy intake and meaningful weight gain, 2) whether the intervention effect was modified by study characteristics or participants' characteristics, and 3) which study or participants' characteristics predict meaningful increase in energy intake and weight among participants from control groups in order to investigate which participants improve nutritional status without receiving any intervention.

2. Materials and methods

2.1. Search strategy

Our search for high quality nutritional intervention studies among older adults was based on two previous published reviews by Milne et al. [8] and de van der Schueren et al. [7]. In addition, we conducted a search in the database of MEDLINE. In the search strategy we combined text words and Medical Subject Headings terms without language restrictions. Search criteria included “nutritional support”, “diet”, “malnutrition”, “undernutrition”, “protein-energy malnutrition”. Furthermore, reference lists of found trials and reviews were searched for possible eligible studies. Only randomized controlled trials (RCTs) were eligible for inclusion.

In addition, studies had to fulfill the following criteria: mean participant age 55 years or older, weight measured at baseline and follow-up, the intervention should aim to increase energy and/or protein intake through dietary counseling, ONS, or the combination of both. Studies were excluded in case of (partial) enteral or parenteral feeding, patients being treated for cancer, and when the nutritional intervention was combined with physical activity (when it was not possible to separate these intervention effects).

2.2. Data extraction and data handling

2.2.1. Study characteristics

Study setting was categorized into hospital, community-dwelling and institution (including nursing homes, homes for older adults, and ‘mixed’ homes). The nutritional interventions (type of intervention) were categorized into dietary counseling (i.e. individualized dietary advice taking into account nutritional status, nutritional rehabilitation goals, participants' (potential) disease status), ONS, or the combination of ONS and dietary counseling.

2.2.2. Participants' characteristics

For the current study we received the following individual participant data from the principle investigators of the included trials: age (y), gender, body height (m), information regarding experienced weight loss 3–6 months prior to study baseline (no weight loss, weight loss < 3.0 kg, weight loss ≥ 3.0 kg, do not know/missing/not assessed), and ONS use compliance (%) for studies including ONS. We also obtained baseline and follow-up values of energy intake (kcal/day), protein intake (g/day), and body weight (kg), from which we calculated the absolute change (follow-up value – baseline value). Body mass index (BMI, weight (kg)/height² (m)) was calculated using baseline height.

2.2.3. Change in total energy intake

Change in total energy intake was categorized into meaningful increase in energy intake. We considered an increase of >250 kcal/day as a meaningful increase in energy intake, as this is related to approximately one bottle of ONS or snack.

2.2.4. Change in body weight

Change in measured body weight was analysed as a categorical variable. To our knowledge, no definition of clinically meaningful weight gain among malnourished older adults is available. Dated studies have shown day-to-day variations in body weight ranging from 0.5 kg to 1.0 kg mainly due to day-to-day variations in body water [21–24]. Therefore, we considered a weight gain of >1.0 kg a meaningful change in body weight as it exceeds its daily fluctuation.

2.3. Statistical analyses

Baseline characteristics are presented as mean values and standard deviations (SDs) for continuous variables and numbers and percentages for categorical variables. To examine the effect of the intervention on meaningful increase in energy intake (>250 kcal/day) and meaningful weight gain (>1.0 kg) (research question 1), we performed logistic generalized estimating equations (GEE) regression analyses, using individual studies as cluster variable. Effect estimates were expressed as odds ratios (ORs) with 95% confidence intervals (95% CI). Besides a crude effect (Model 1), we also analysed the effect adjusted for age, sex, BMI at baseline, weight loss prior to study baseline, and study setting (Model 2). In a subsample of participants with baseline intake data ($n = 734$), adjustments for baseline energy and protein intake was done. Additionally, we examined the moderating effect of study

characteristics and participants' characteristics (research question 2), by adding the interaction terms separately to the crude model, with a P -value < 0.10 considered to be statistically significant for the interaction terms. In order to investigate which variables were possible predictors for meaningful increase in energy intake and meaningful weight gain among participants from the control group (research question 3), we also performed GEE regression analyses. All possible predictor variables, both study characteristics as well as participants' characteristics, were included in one model restricted to control group participants. Backwards selection procedure with a significance level of 0.05 was performed. Effect estimates were expressed as ORs with 95% CIs.

In sensitivity analyses, we considered being weight stable during the study (no difference in weight between baseline and follow-up weight) as a benefit among those who reported weight loss prior to baseline, in addition to >1.0 kg weight gain in those without weight loss prior to baseline. This was considered as a positive weight course. Furthermore, to test the robustness of the observed associations, weight gain of >2.0 kg during the study was considered as a significant benefit, as well as an increase in energy intake of >500 kcal/day.

Analyses were performed with IBM SPSS Statistics for Windows, version 23.0 (Armonk, NY: IBM Corp). A two-sided P -value < 0.05 was considered statistically significant.

3. Results

We identified 38 nutritional intervention studies that met our inclusion criteria. For eight studies, no contact information was available. Of the remaining 30 studies the principal investigators were contacted for contribution to the current study. Reasons for not contributing were as follows; no response ($n = 6$), data had been destroyed ($n = 6$), not able to provide the data ($n = 5$), not applicable (e.g. when it was not possible to separate intervention groups when a combined intervention was performed for exercise and nutrition) ($n = 3$), or studies were performed using the same dataset ($n = 1$). Therefore, the current study includes data from nine nutritional intervention studies with a total of 1265 participants [13,18,19,25–30]. A flow diagram for the identification process can be found in the Supplemental Fig. 1. Participants were included in the current study when data on age, baseline BMI, and change in body weight during follow-up were available, which resulted in 990 participants in the final pooled analytical dataset. From those, data on change in energy intake was available for 690 participants. Table 1 presents the characteristics of the included nutritional intervention studies and their inclusion criteria. Supplemental Table 1 presents participants' baseline characteristics of each included nutritional intervention study.

3.1. Study characteristics

Four studies were performed in a hospital setting including older adults at discharge from hospital [13,18,25,30], three studies among community-dwelling older adults [19,26,29], and two studies among institutionalized older adults [27,28]. Participants in the intervention group ($n = 500$, 50.5%) were more often included in an institutionalized setting than participants in the control group ($n = 490$, 49.5%), which is due to a slight oversampling of participants in the intervention group in one study conducted in an institutionalized setting [27], and oversampling of participants in the control group in one study conducted in a hospital setting [30] (Table 2). Risk of malnutrition was based on NRS2002 [18,25], MNA-sf screening tool [28,30], low BMI or recent weight loss [13,26], SNAQ⁶⁵⁺ [19], the Fried criteria [29], or no malnutrition criterion was applied [27]. In four studies, the intervention consisted of dietary counseling [18,19,25,30], in four

studies the intervention consisted of providing ONS only [26–29], and in one study the intervention consisted of ONS in combination with dietary counseling [13] (Table 1). In studies providing dietary counseling, ONS were provided only if the intake of regular foods and beverages was insufficient. Regarding studies providing ONS alone; Manders et al. [27], and Stange et al. [28] provided nutrient- and energy-dense dairy drink, de Jong et al. [26] provided fortified milk and fruit drinks, and Tieland et al. [29] provided protein enriched drinks. The duration of the studies ranged from 12 weeks up to 6 months, with three studies lasting 12 weeks [18,25,28]; three studies lasting 17 weeks/3 months [13,19,26] and three studies lasting 6 months [27,29,30]. Data on compliance of ONS was available in all studies providing ONS alone and in one (out of one) study on ONS in combination with dietary counseling [13,26–29]. Mean compliance to ONS (intervention group) was 74.1%, whereby compliance in the hospital (80.0%) and community-dwelling setting (90.6%) was significantly higher compared to the compliance of studies performed among institutionalized older adults (61.2%) (P -value < 0.001).

3.2. Participants' characteristics

Mean age of participants in the pooled dataset was 79.2 ± 8.2 years, 64.5% were women and mean BMI at baseline was 23.9 ± 4.7 kg/m² (Table 2). Participants in the intervention group experienced more often weight loss prior to study baseline and had a higher energy intake at baseline compared to participants in the control group. No significant differences between intervention and control group were observed at baseline for other participants' characteristics.

3.3. Change in energy intake

Seven out of nine studies [13,18,19,25,26,29,30] had data on energy intake at both baseline and at follow-up ($n = 690$). These studies were only performed in a hospital setting or among community-dwelling older adults. Energy intake was assessed by means of a dietary record [13,19,25,26,29], a food frequency questionnaire [30], or a four day dietary record [18]. Mean energy intake increased by 164 ± 636 kcal/day in the intervention group and by 72 ± 535 kcal/day in the control group. Participants in the intervention group ($n = 138$, 41.4%) had more often a meaningful increase in energy intake (defined as >250 kcal/day) compared to participants in the control group ($n = 112$, 31.4%). Table 3 shows baseline characteristics according to meaningful increase in energy intake.

Compared to the control group, the intervention group had a non-significant increased odds of meaningful increase in energy intake OR: 1.59 (95% CI 0.95, 2.66) (Model 1), which remained non-significant in the adjusted model OR: 1.64 (95% CI 0.97, 2.79) (Model 2, Fig. 1A). Additional adjustment for baseline energy and protein intake resulted in a more pronounced intervention effect; OR: 2.13 (95% CI 1.47, 3.10).

A significant interaction (P -value < 0.1) of the intervention effect with sex, baseline age and baseline BMI, with age and BMI both included as continuous variables was observed. The intervention effect was greater for women, those at higher age, and those with lower BMI.

Stratifying the analyses by type of intervention showed that, compared to the control group, a non-significant intervention effect on increase in energy intake was observed for dietary counseling (OR: 1.83; 95% CI 0.89, 3.73), a negative intervention effect for ONS alone (OR: 0.60; 95% CI 0.54, 0.67), while a positive intervention effect was observed for dietary counseling in combination with ONS (OR: 2.28; 95% CI 1.90, 2.73) (Fig. 1B) after adjustment for age, sex, BMI at baseline, weight loss prior to study baseline, and study

Table 1
Characteristics of the included nutritional intervention studies and their inclusion criteria^a.

Reference (#)	Number of participants (control/intervention)	Age inclusion criteria (y)	Malnutrition inclusion criteria (when applicable)	Setting
Beck et al. 2013 [25]	58/61	>65	BMI < 20.5 kg/m ² ; and/or weight loss within the last three months; and/or a reduced dietary intake in the last week; and/or serious ill. (Level 1 screening NRS2002)	Geriatric patients at hospital discharge.
Beck et al. 2015 [18]	29/29	>70	Level 2 screening in NRS2002 (weight loss > 5% previous two months or BMI 18.5–20.5 kg/m ² + impaired general condition or food intake 25–50% of normal requirement in preceding week, or major disease); receiving nutritional support by means of small volume commercial ONS; and to be discharged to their private home assisted by the discharge Liaison-Team.	Geriatric patients at hospital discharge.
Feldblum et al., 2011 [30]	124/68	≥65	Malnutrition according to the MNA-sf screening tool (score < 10) or based on self-report weight loss of more than 10% during the 6 months before the study period.	Older patients at internal medicine departments.
de Jong et al. 2000 [26]	38/41	≥70	Lack of regular exercise, BMI ≤ 25 kg/m ² or recent weight loss, and no use of multivitamin supplements.	Community-dwelling older adults with need for medical home care, use of meals-on-wheels service, or household assistance.
Manders et al. 2009 [27]	43/93	>60	No inclusion criteria with regard to nutritional status.	Nursing homes residents.
Neelemaat et al. 2011 [13]	71/71	≥60	Malnourished according to the following criteria: BMI < 20.0 kg/m ² or lower and/or 5% or more unintentional weight loss in the previous month and/or 10% or more unintentional weight loss in the previous 6 months.	Hospital-admitted older patients.
Schilp et al. 2013 [19]	62/64	≥65	Malnourished according to the SNAQ ⁶⁵⁺ screening tool; mid-upper arm circumference < 25 cm and/or self-report of ≥ 4 kg unintentional weight loss within the past 6 months.	Community-dwelling older adults.
Stange et al. 2013 [28]	36/42	—	Malnourished according to the MNA screening tool; participants with a score below 24 points, a BMI of ≤ 22 kg/m ² , a low food intake according to the nurses' perception, or weight loss of 5% or more in the past 3 months or 10% or more in the past 6 months.	Nursing home residents.
Tieland et al. 2012 [29]	29/31	≥65	Pre-frail and frail according to the Fried criteria; (1) unintentional weight loss, (2) weakness, (3) self-reported exhaustion, (4) slow walking speed, and (5) low physical activity. Subjects were considered pre-frail when 1 or 2 criteria were applicable and frail when 3 or more criteria were present.	Community-dwelling older adults.
Intervention		Control		Follow-up duration used
Beck et al. 2013 [25]	<ul style="list-style-type: none"> Three follow-up visits by general practitioners complemented with three follow-up visits by a dietitian in order to make a personalized nutrition care plan. ONS if needed. 	<ul style="list-style-type: none"> Three follow-up visits by general practitioners; ONS if needed. 		12 weeks
Beck et al. 2015 [18]	<ul style="list-style-type: none"> Liaison-Team in cooperation with a dietitian. A Liaison-Team facilitates the transition of older patients from hospital to private home, i.e. follow-up on the medical treatment, the need for change in use of social services (home care, meals-on-wheels, home, home nursing). ONS if needed. 	<ul style="list-style-type: none"> Liaison-Team; ONS if needed. 		12 weeks
Feldblum et al. 2011 [30]	<ul style="list-style-type: none"> Dietetic treatment from a qualified trained dietitian in the hospital and three home visits after discharge. ONS if needed. 	<ul style="list-style-type: none"> Usual care; which included dietitian services upon request; ONS if needed. 		6 months
de Jong et al. 2000 [26]	<ul style="list-style-type: none"> Two supplemental nutrient-dense products per day (1 from a series of fruit products (100 g) and 1 from a series of dairy products (75 g)) (total of 115 kcal). 	<ul style="list-style-type: none"> Regular products (vitamins and minerals at the highest 15% of the concentration in enriched products) (total of 115 kcal). 		17 weeks
Manders et al. 2009 [27]	<ul style="list-style-type: none"> Two supplemental nutrient-enriched drinks (125 mL) per day (total of 250 kcal, 8.75 g protein) 	<ul style="list-style-type: none"> A placebo drink containing no energy, vitamins or minerals. 		24 weeks
Neelemaat et al., 2011 [13]	<ul style="list-style-type: none"> Energy and protein enriched diet (during the in-hospital period); Two supplemental servings per day of ONS (total of 600 kcal, 24 g protein); Supplement of 400 IE vitamin D3 and 500 mg calcium per day Telephone counseling by a dietitian. 	<ul style="list-style-type: none"> Usual care; they were given nutritional support only on prescription by their treating physician. 		3 months

Table 1 (continued)

	Intervention	Control	Follow-up duration used
Schilp et al. 2013 [19]	<ul style="list-style-type: none"> • Dietetic treatment from a qualified trained dietitian; • Supplement of 1000 mg calcium and 800 IU vitamin D per day; • ONS if needed. 	<ul style="list-style-type: none"> • Usual care and was not referred to a dietitian through the study, ONS if needed; • Received standard brochure of the Netherlands Nutrition Centre with general information about healthy eating habits; • Supplement of 1000 mg calcium and 800 IU vitamin D/day. 	3 months
Stange et al. 2013 [28]	<ul style="list-style-type: none"> • Two supplemental servings per day of ONS (total of 600 kcal, 24 g protein); • Care personnel were instructed to encourage residents to consume the amount offered, and to support compliance. 	<ul style="list-style-type: none"> • Usual care, which included provision of homemade snacks or ONS when prescribed by the physician or provided by family members. 	12 weeks
Tieland et al. 2012 [29]	<ul style="list-style-type: none"> • Two supplemental beverage per day (250-mL) (total of 95 kcal, 15 g protein). 	<ul style="list-style-type: none"> • Two supplemental servings per day of a placebo supplement of 250-mL beverage containing no protein (30 kcal). 	24 weeks

Abbreviations: C, control group; I, intervention group; MNA, Mini Nutritional Assessment; MNA-sf, Mini Nutritional Assessment-short form; NRS2002, Nutritional Risk Screening 2002; ONS, Oral Nutritional Supplements; SGA, Subjective Global Assessment; SNAQ65+, Short Nutritional Assessment Questionnaire 65+.

^a Information is presented for participants with complete baseline and follow-up data ($n = 990$).

setting. The effectiveness of dietary counseling on energy intake was not significantly different compared to dietary counseling in combination with ONS (P -value = 0.49), however, dietary counseling and dietary counseling in combination with ONS had a greater effect on energy intake compared to ONS alone (P -value = 0.002 and P -value < 0.001 respectively).

Applying a more robust cut-off value of >500 kcal/day, 63 (17.6%) participants in the control group, 41 (20.1%) participants in the intervention group receiving dietary counseling, 4 (5.7%) participants in the intervention group receiving ONS alone, and 33 (55.9%) participants receiving dietary counseling in combination with ONS had a meaningful increase in energy intake. Compared to the control group and adjusted for age, sex, BMI at baseline, weight loss prior to study baseline and study setting, a non-significant overall intervention effect was observed (OR: 1.49; 95% CI 0.92, 2.42).

3.4. Change in weight

Mean weight change was higher in the intervention group (0.79 ± 3.86 kg) compared to the control group (0.06 ± 4.70 kg) including data from all 9 studies. Similarly, the number of

participants with meaningful weight gain (>1.0 kg) was higher in the intervention group ($n = 221, 44.2\%$) compared to the control group ($n = 168, 34.3\%$). Meaningful weight gain (>1.0 kg) was more often observed among participants who increased their energy intake ($n = 122, 48.8\%$) compared to participants who did not meaningfully increase energy intake ($n = 156, 35.5\%$). Baseline characteristics according weight gain status are presented in Table 3. Crude analyses showed that participants in the intervention group had an increased odds of meaningful weight gain compared to participants in the control group; OR: 1.58 (95% CI 1.16, 2.17) (Model 1). Adjusting for age, sex, BMI at baseline, weight loss prior to study baseline, and study setting (Model 2) resulted in a more pronounced intervention effect; OR: 1.67 (95% CI 1.21, 2.30) (Fig. 2A). Additional adjustments for baseline energy and protein showed a similar intervention effect (Model 2, OR: 1.59; 95% CI 1.09, 2.32 vs. Model 2 + intake, OR: 1.55; 95% CI 1.05, 2.30).

There was no significant interaction for intervention effect on weight gain with age, sex, BMI at baseline or setting (P -values of the interaction terms were all >0.4), suggesting that participants' characteristics and setting did not modify the intervention effect.

Table 2

Baseline characteristics of all pooled participants participating in randomized controlled nutritional intervention trials, and according to control vs. intervention group.

	Total sample $n = 990$	Control $n = 490$ (49.5%)	Intervention $n = 500$ (50.5%)
Setting			
Hospital	511 (51.6)	282 (57.6)	229 (45.8)
Community-dwelling	265 (26.8)	129 (26.3)	136 (27.2)
Institutionalized	214 (21.6)	79 (16.1)	135 (27.0)
Type of intervention			
Dietary counseling			222 (44.4)
ONS			207 (41.4)
Dietary counseling + ONS			71 (14.2)
Age	79.2 ± 8.2	78.8 ± 8.3	79.6 ± 8.1
Sex (% women)	639 (64.5)	311 (63.5)	328 (65.6)
BMI baseline	23.9 ± 4.7	23.9 ± 4.8	23.9 ± 4.5
BMI groups			
<22.0 kg/m ²	364 (36.8)	180 (36.7)	184 (36.8)
22.1–28.0 kg/m ²	457 (46.2)	218 (44.5)	239 (47.8)
>28.0 kg/m ²	169 (17.1)	92 (18.8)	77 (15.4)
Weight loss experienced prior to baseline			
No	136 (13.7)	72 (14.7)	64 (12.8)
Yes	269 (27.2)	150 (30.6)	119 (23.8)
Do not know/missing/not assessed	585 (59.1)	268 (54.7)	317 (63.4)
Energy intake at baseline (kcal/day) ^a	1577 ± 579	1526 ± 562	1634 ± 594
Protein intake at baseline (g/day) ^a	61.8 ± 25.7	60.2 ± 25.5	63.4 ± 25.9

Values are mean \pm SDs or numbers (%).

Abbreviation: ONS, Oral Nutritional Supplements.

^a Available for $n = 386$ in the control group and $n = 348$ in the intervention group [13,18,19,25–30].

Table 3
Baseline characteristics for participants participating in randomized controlled nutritional intervention trials according to meaningful increase in energy intake (>250 kcal/day) and according to meaningful weight gain (>1.0 kg) during the intervention period.

	No meaningful increase in energy intake (≤ 250 kcal/day) <i>n</i> = 440 (63.8%)	Meaningful increase in energy intake (>250 kcal/day) <i>n</i> = 250 (36.2%)	No meaningful weight gain (≤ 1.0 kg during intervention period) <i>n</i> = 601 (60.7%)	Meaningful weight gain (>1.0 kg during intervention period) <i>n</i> = 389 (39.3%)
Treatment group				
Control	245 (55.7)	112 (44.8)	322 (53.6)	168 (43.2)
Intervention	195 (44.3)	138 (55.2)	279 (46.4)	221 (56.8)
Setting				
Hospital	245 (55.7)	192 (76.8)	282 (46.9)	229 (58.9)
Community-dwelling	195 (44.3)	58 (23.2)	183 (30.4)	82 (21.1)
Institutionalized	—	—	136 (22.6)	78 (20.1)
Type of intervention				
Dietary counseling	281 (63.9)	152 (60.8)	309 (51.4)	186 (47.8)
ONS	113 (25.7)	21 (8.4)	232 (38.6)	121 (31.1)
Dietary counseling + ONS	46 (10.5)	77 (30.8)	60 (10.0)	82 (21.1)
Age (years)	78.6 \pm 7.6	77.2 \pm 8.1	79.9 \pm 8.0	78.2 \pm 8.4
Sex (% women)	285 (64.8)	137 (54.8)	404 (67.2)	235 (60.4)
BMI baseline (kg/m ²)	24.0 \pm 4.9	23.0 \pm 4.6	24.0 \pm 4.5	23.7 \pm 5.0
BMI groups				
<22.0 kg/m ²	157 (35.7)	113 (45.2)	213 (35.4)	151 (38.8)
22.1–28.0 kg/m ²	202 (45.9)	106 (42.4)	281 (46.8)	176 (45.2)
>28.0 kg/m ²	81 (18.4)	31 (12.4)	107 (17.8)	62 (15.9)
Weight loss experienced prior to baseline				
No	35 (8.0)	26 (10.4)	89 (14.8)	47 (12.1)
Yes	119 (27.0)	93 (37.2)	130 (21.6)	139 (35.7)
Do not know/missing	286 (65.0)	131 (52.4)	382 (63.6)	203 (52.2)
Energy intake at baseline (kcal/day) ^a	1727 \pm 572	1353 \pm 519	1547 \pm 558	1622 \pm 609
Protein intake at baseline (g/day) ^a	68.2 \pm 26.1	51.5 \pm 21.8	60.4 \pm 24.5	63.8 \pm 24.0

Values are mean \pm SDs or numbers (%).

Abbreviation: ONS, Oral Nutritional Supplements.

^a Available for *n* = 439 in the 'no meaningful weight gain group' and *n* = 295 in the 'meaningful weight gain group'.

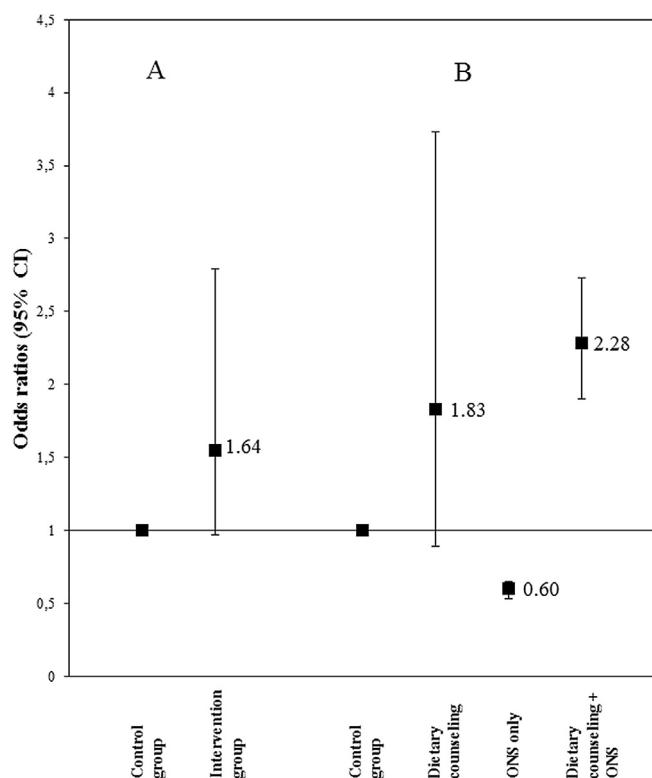


Fig. 1. Total intervention effect (A) and specified for type of intervention (B) (dietary counseling, *n* = 204; ONS, *n* = 70, or a combination of both, *n* = 59, versus control group, *n* = 357) on meaningful increase in energy intake (>250 kcal/day) among 690 older adults. Graphic representation of odds ratios, adjusted for age, sex, BMI at baseline, weight loss prior to study baseline and study setting, from GEE analyses using individual studies as cluster variable.

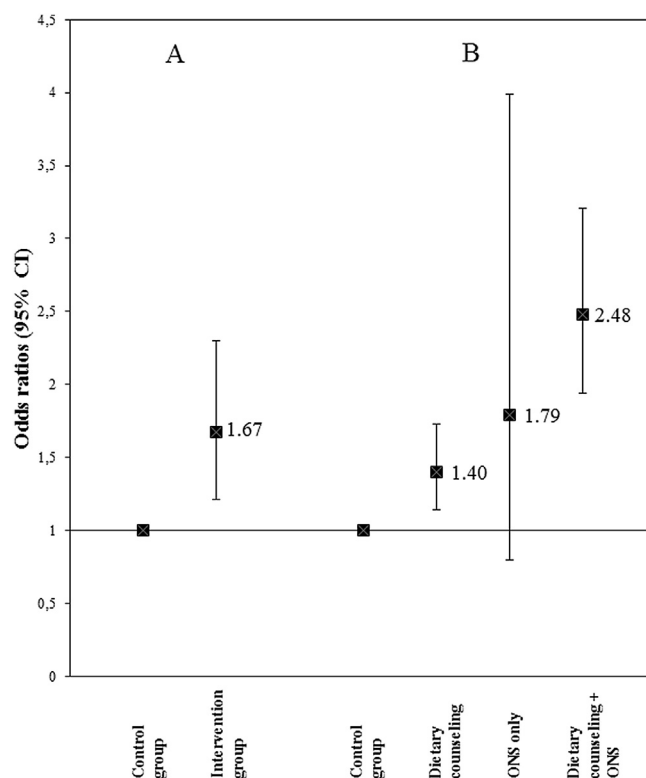


Fig. 2. Total intervention effect (A) and specified for type of intervention (B) (dietary counseling, *n* = 222; ONS, *n* = 207, or a combination of both, *n* = 71, versus control group, *n* = 490) on meaningful weight gain (>1.0 kg) among 990 older adults. Graphic representation of odds ratios, adjusted for age, sex, BMI at baseline, weight loss prior to study baseline and study setting, from GEE analyses using pooled data from 10 intervention studies and individual studies as cluster variable.

Table 4

Baseline characteristics for participants in the control group according to meaningful increase in energy intake (>250 kcal/day) ($n = 357$) and meaningful weight gain (>1.0 kg) ($n = 490$) during the study period.

	No meaningful increase in energy intake (≤ 250 kcal/day) $n = 245$ (68.6%)	Meaningful increase in energy intake (>250 kcal/day) $n = 112$ (31.4%)	<i>P</i> -value	No meaningful weight gain (≤ 1.0 kg during intervention period) $n = 322$ (65.7%)	Meaningful weight gain (>1.0 kg during intervention period) $n = 168$ (34.3%)	<i>P</i> -value
Setting			<0.001			0.020
Hospital	145 (59.2)	88 (78.6)		171 (53.1)	111 (66.1)	
Community-dwelling	100 (40.8)	24 (21.4)		92 (28.6)	37 (22.0)	
Institutionalized	—	—		59 (18.3)	20 (11.9)	
Age	78.9 \pm 7.7	75.8 \pm 8.3	0.001	79.6 \pm 8.3	77.3 \pm 8.2	0.003
Sex (% women)	159 (64.9)	57 (50.9)	0.012	212 (65.8)	99 (58.9)	0.132
BMI baseline	23.9 \pm 4.9	23.4 \pm 4.9	0.430	24.0 \pm 4.5	23.9 \pm 5.4	0.827
BMI groups			0.709			0.687
<22.0 kg/m ²	93 (38.0)	44 (39.3)		117 (36.3)	63 (37.5)	
22.1–28.0 kg/m ²	106 (43.3)	51 (45.5)		141 (43.8)	77 (45.8)	
>28.0 kg/m ²	46 (18.8)	17 (15.2)		64 (19.9)	28 (16.7)	
Weight loss experienced prior to baseline			0.021			0.001
No	23 (9.4)	12 (10.7)		55 (17.1)	17 (10.1)	
Yes	69 (28.2)	47 (42.0)		82 (25.5)	68 (40.5)	
Do not know/missing	153 (62.4)	53 (47.3)		185 (57.5)	83 (49.4)	
Energy intake at baseline (kcal/day) ^a	1667 \pm 543	1269 \pm 509	<0.001	1504 \pm 576	1564 \pm 534	0.314
Protein intake at baseline (g/day) ^a	66.4 \pm 25.2	48.5 \pm 22.3	<0.001	59.0 \pm 25.6	62.4 \pm 25.3	0.209

Values are mean \pm SDs or numbers (%).

Abbreviation: ONS, Oral Nutritional Supplements.

^a Available for $n = 247$ in the 'no meaningful weight gain group' and $n = 139$ in the 'meaningful weight gain group'.

Stratifying the analyses by type of intervention showed that, compared to the control group, an intervention effect on meaningful weight gain was observed for dietary counseling (OR: 1.40; 95% CI 1.14, 1.73) and dietary counseling in combination with ONS (OR: 2.48; 95% CI 1.92, 3.31). In contrast, the OR for ONS alone was not significant (OR: 1.79; 95% CI 0.80, 3.99) (Fig. 2B). Dietary counseling in combination with ONS had a larger intervention effect on meaningful weight gain compared to dietary counseling alone (P -value < 0.001), but no statistically significant greater effect compared to ONS alone (P -value = 0.54). In addition, no statistically significant difference in intervention effect was observed for dietary counseling compared to ONS alone (P -value = 0.55).

In sensitivity analyses, we investigated the intervention effect on positive weight course (i.e. being weight stable during the study as a meaningful weight benefit among those who reported weight loss prior to baseline, in addition to >1.0 kg weight gain in those without weight loss prior to baseline). This resulted in 456 participants (46.1%) with a positive weight course, and 543 participants (53.9%) who lost weight or gained ≤ 1.0 kg weight (among participant with no experienced weight loss prior to baseline). Using this alternative definition for a positive weight course, participants in the intervention group were more often meaningful weight gainers ($n = 244$, 48.8%) compared to participants in the control group ($n = 212$, 43.3%). Logistic GEE analyses showed that the intervention effect was somewhat attenuated compared to the main results, but still significant: OR 1.36 (95% CI 1.00; 1.84) (Model 1), and OR 1.49 (95% CI 1.07; 2.06) (Model 2).

The number of participants with meaningful weight gain defined as >2.0 kg was higher in the intervention group ($n = 155$, 31.0%) compared to the control group ($n = 114$, 23.3%). A total of 65 (29.3%) participants in the intervention group receiving dietary counseling, 55 (26.6%) participants in the intervention group receiving ONS alone, and 35 (49.3%) participants receiving dietary counseling in combination with ONS increased >2.0 kg body weight during the study period. Compared to the control group, a significant intervention effect on >2.0 kg weight gain was observed (OR: 1.69; 95% CI 1.20, 2.36), after adjustment for age, sex, BMI at baseline, weight loss prior to study baseline and study setting.

3.5. Predictors of meaningful increase in energy intake and meaningful weight gain and among participants in the control group

Table 4 presents baseline characteristics from the control group who meaningfully increased energy intake or meaningfully gained weight, and those who did not. The predictors for meaningful increase in energy intake were; lower age (OR: 1.04; 95% CI 1.02, 1.05), male gender (OR: 1.75; 95% CI 1.03, 2.97), being hospitalized (compared to community-dwelling) (OR: 2.44; 95% CI 1.20, 5.00), and no reported weight loss compared to >3.0 kg weight loss prior to study baseline (OR: 1.23; 95% CI 1.06, 1.43). Analyses with adjustments for baseline energy and protein intake showed that lower age (OR: 1.05; 95% CI 1.03, 1.09), male gender (OR: 3.33; 95% CI 1.57, 7.09), and lower baseline energy intake (per 100 kcal) (OR: 1.22; 95% CI 1.14, 1.31) were significant predictors for meaningful increase in energy intake.

Predictors for meaningful weight gain were; >3.0kg weight loss prior to study baseline compared to no reported weight loss (OR: 2.60; 95% CI 1.59, 4.23), and study setting (community-dwelling (OR: 0.76; 95% CI 0.62, 0.94) or institutionalized (OR: 0.72; 95% CI 0.59, 0.88) were less likely to experience meaningful weight gain compared to those who were hospitalized). When performing these analyses with additional adjustments for baseline energy and protein intake in the subsample with baseline data on intake ($n = 386$), significant predictors remained the same; >3.0 kg weight loss prior to study baseline compared to no reported weight loss (OR: 2.28; 95% CI 1.70, 3.06), and study setting (community-dwelling; OR: 0.77; 95% CI 0.65, 0.91, compared to a hospital setting).

4. Discussion

In this pooled analyses of individual data from nine international nutritional intervention studies in older adults at risk of malnutrition, we observed a positive intervention effect of nutritional intervention on energy intake and body weight versus control (research question 1). There was a positive intervention effect on both outcomes for providing dietary counseling and for providing dietary counseling with ONS, but not for providing ONS

alone. Participants' characteristics did not modify the intervention effect for meaningful weight gain, while the intervention effect on meaningful increase in energy intake was greater for women, those at higher age, and those with lower baseline BMI (research question 2). We also observed that, among participants who did not receive any nutritional intervention (control group), predictors for meaningful increase in energy intake were lower age, male gender, being hospitalized, and no weight loss prior to baseline, while weight loss prior to study baseline and a hospital setting were predictors for meaningful weight gain (research question 3).

Milne et al. (2009) published a systematic review and meta-analyses regarding the effectiveness of protein and energy supplementation (with or without dietary counseling) in older adults at risk of malnutrition, though studies of dietary counseling alone were not included [8]. Authors concluded that supplementation results in a small weight gain of 2.2%, and an intervention effect on complications and mortality in those who were undernourished. Another meta-analyses showed beneficial intervention effects on clinical, functional and nutritional outcomes of high protein ONS compared to placebo, routine care, normal diet, dietary advice, or ONS not high in protein [31]. Baldwin et al. [9] recently reviewed the effects of supportive interventions for enhancing dietary intake among adults who were (at risk of) malnutrition. Authors concluded that there is moderate-quality evidence that supportive interventions improve nutritional status such as minimal weight gain or energy intake. Elia et al. reviewed the association and effect of standard ONS on health (care) outcomes in a hospital setting [32], and in the community and home care settings [33]. The review showed that ONS in a hospital setting is associated with lower mortality risk, fewer complications and shorter length of stay [32], and that ONS in the community and home care settings is associated with increased weight, skinfold thickness and mid-arm muscle circumference, improved nutritional status, and lower hospitalization [33]. However, in the analyses, authors did not take into account whether studies included dietary counseling or not. The results of these previous meta-analyses are not fully confirmed by our pooled individual data analyses. Dietary counseling with and without ONS showed a positive effect on increase in energy intake and weight gain, while the effect for ONS alone was reversed and not statistically significant. A possible explanation why (protein rich) ONS alone showed a reversed effect on meaningful increase in energy intake could be that participants compensated their habitual energy intake or had a different appetite level which has been observed in some [34,35] but not all studies [36,37]. Another possible explanation is that studies included in those analyses, i.e. with data on nutritional intake, primary aimed to investigate effects of resistance-type exercise training with or without additional dietary protein [26,29]. In that case, we included the protein and control groups only. Studies were aimed to increase muscle mass and strength [29] or improve micronutrient level [26], and not necessarily increase in energy intake or body weight. Another possible explanation of discrepancies in previously published results regarding effects of ONS alone and our results could be differences in age range, as we only included studies performed in older persons, whereas in the previous meta-analyses participants aged 18 years and older were included [9].

A unique aspect of our study, that could not be addressed in the previous reviews [8,9,31–33], is that we were able to investigate whether intervention effects were influenced by study characteristics or participants' characteristics, specified to older adults. We observed that the intervention was more effective on increasing energy intake among women, those at higher age and those with a lower BMI. Although this interaction effect was not found for meaningful weight gain, these results suggest that females, those who are older and more underweight are more likely to respond to

the intervention by increasing their energy intake. Future studies should investigate the mechanisms explaining these interaction effects.

Another unique aspect of this study is the ability to test the actual effect of the intervention on energy intake. Milne et al. [8] suggest that an increase of 400 kcal/day results in a modest positive effect on weight gain. Unfortunately, most previous studies reported the amount of kilocalories provided through ONS and not the actual total amount of kilocalories consumed per day. It is possible that participants who received ONS compensated by reducing the intake of meals and snacks. This current study shows that the intervention group on average consumed more calories compared to the control group, suggesting that they did not completely compensate the energy supplemented. Moreover, participants who meaningfully increased their energy intake, more often were meaningful weight gainers, suggesting again an overall increase in the daily energy intake.

Next to investigating the effect of nutritional intervention, we also investigated which study and participants' characteristics predicted improved nutritional status in those without any intervention (control group). We showed that lower age, male gender, a hospital setting and no reported weight loss at study baseline were predictors for meaningful increase in energy intake, and that reported weight loss at study baseline and a community-dwelling or institutionalized setting were predictors for a meaningful increase in body weight. This could be explained by the fact that younger adults are more resilient compared to older adults [38]. Hospitalized older adults, compared to community-dwelling and institutionalized older adults, are often recovering from acute illness during the nutritional intervention, and this recovery itself may already have a positive effect on their energy intake and body weight, which could explain why the ample majority of the participants in the control group who meaningfully increased energy intake or meaningfully gained weight were hospitalized. Reporting weight loss prior to study baseline was a predictor for not increasing energy intake. It is possible that those participants were more often severely diseased and suffered from a poorer appetite. A poorer appetite in turn is linked to a lower energy intake and is likely to result in weight loss. Based on these analyses among participants from the control group, we can conclude that women, those with a higher age, and depending on the setting and their weight loss status, need active treatment since their likelihood of natural recovery is lower.

In our study, body weight was used as outcome measure. It is however possible that nutritional interventions do not result in a meaningful weight gain, but could lead to other clinical benefits such as functional benefits. This could occur through an improvement in micronutrient levels or body composition (i.e. an increase in lean body mass). Future studies using pooled datasets are needed to investigate the effect of nutritional interventions on other health outcomes, such as muscle mass, muscle strength, physical function and survival.

4.1. Strength and limitations

A major strength of this study is the availability of individual study participant data from nine high-quality, randomized controlled intervention studies. This has resulted in greater statistical power compared to previous meta-analyses, and allows investigating whether intervention effect was influenced by study characteristics or participants' characteristics. Furthermore, this study was unique in the ability to investigate the intervention effects on actual energy intake. However, this study is not without limitations. Our literature search yielded in 38 articles, of which we were able to retrieve data from nine studies. Reason for not

contributing in the current study were mainly because no contact information was available or data from older studies were already destroyed. This might have led to selection bias towards more recent trials. Furthermore, the ample majority of the included studies were conducted in Europe. Another limitation is that we were not able to investigate whether the effect of a specific treatment differed between the three study settings since the three intervention types were not performed in all study settings. Furthermore, the included studies differed according to the method used to assess nutritional intake (dietary records, frequency questionnaire, and dietary history). However, since we analysed change in energy intake within persons, the impact of combining data from these different methods might be limited. In addition, we analysed change in energy intake from baseline to the end of the intervention period to assess the effect of the intervention. We cannot exclude that this approach may have led to an underestimation of the true effect of the intervention on energy intake, since the effect might have faded out over time. However, three included studies with multiple measurements of energy intake [19,29,30], showed that increase in energy intake from baseline to mid-intervention was not greater compared to the increase from baseline to the end of the intervention period, suggesting that the potential underestimation of the effect is limited.

5. Conclusions

We conclude that nutritional interventions are effective in increasing energy intake and body weight among older adults at risk of malnutrition. Dietary counseling with or without ONS was more effective compared to ONS alone, which shows the importance of active dietary counseling in the treatment of (risk of) malnutrition in older adults. The intervention effect on meaningful increase in energy intake was greater for women, those at higher age, and those with lower baseline BMI. Among participants who did not receive any nutritional intervention, lower age and a hospital setting were predictors for meaningful weight gain, whereas lower age, male gender, a hospital setting and no weight loss prior to baseline were predictors for meaningful increase in energy intake. Future studies should focus on investigating the effectiveness of different nutritional interventions on other clinically relevant outcomes, such as body composition, muscle strength, physical function and survival in different health care settings.

Authors contribution

The authors' contributions were as follows; IR, DV and MV designed the research; IR collected, pooled and analysed the data and wrote the manuscript; MV had the primary responsibility for the final content; JWRT assisted with the statistical analyses; LCPGMG, AMB, MAES, DRS, HAHW, DV and MV conducted the original studies and provided data; all authors read and approved the final manuscript.

Conflicts of interest

The authors declare that they do not have conflict of interest.

Funding sources

This work was initiated by the Joint Programming Initiative 'A Healthy Diet for a Healthy Life'. The funding agencies supporting the MaNuEL Knowledge Hub are (in alphabetical order of participating Member State): Austria: Federal Ministry of Science, Research and Economy; France: Ecole Supérieure d'Agricultures (ESA); Germany: Federal Ministry of Food and Agriculture

represented by Federal Office of Agriculture and Food; Ireland: Department of Agriculture, Food and the Marine, and the Health Research Board; Spain: Instituto de Salud Carlos III, and the SENATOR trial (FP7-HEALTH-2012-305930); The Netherlands: The Netherlands Organisation for Health Research and Development (ZonMw).

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.clnu.2018.07.023>.

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